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Review

Effect of Orthopedic Treatment for Class III Malocclusion on Upper Airways: A Systematic Review and Meta-Analysis

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Abstract: The aim of this systematic review is to compare the effect on the upper airways of orthopedic treatment for skeletal Class III malocclusion with untreated controls. Nine databases were searched up to August 2020 for randomized or nonrandomized clinical trials comparing orthopedic Class III treatment (facemask or chin-cup) to untreated Class III patients. After duplicate study selection, data extraction, and risk of bias assessment (Risk Of Bias In Non-randomized Studies - of Interventions [ROBINS-I]), random-effects meta-analyses of Mean Differences (MDs)/Standardized Mean Differences (SMD) and 95% Confidence Intervals (CIs) were performed, followed by the Grading of Recommendations Assessment, Development and Evaluation assessment evidence-quality. A total of 10 papers (9 unique nonrandomized studies) with 466 patients (42.7% male; average age 9.1 years) were finally included. Limited evidence indicated that compared to normal growth, maxillary protraction with facemask was associated with increases in total airway area ($n = 1$; MD = 222.9 mm²; 95% CI = 14.0–431.7 mm²), total nasopharyngeal area ($n = 4$; SMD = 1.6; 95% CI = 1.2–2.0), and individual airway dimensions (upper-airway MD = 2.5 mm; lower-airway MD = 2.1 mm; upper-pharynx MD = 1.6 mm; lower-pharynx MD = 1.0 mm; all $n = 6$). Subgroup/meta-regression analyses did not find any significant effect-modifiers, while the results were retained 2–5 years postretention. Our confidence in these estimates was, however, very low, due to the inclusion of nonrandomized studies with methodological issues. Limited data from 2 chin-cup studies indicated smaller benefits on airway dimensions. Existing evidence from controlled clinical studies on humans indicates that maxillary protraction for skeletal Class III treatment might be associated with increased airway dimensions, which are, however, mostly minor in magnitude.

Keywords: class III malocclusion; maxillary retrognathism; orthopedic treatment; dentofacial orthopedics; orthodontics; clinical trials; systematic review; meta-analysis

1. Introduction

1.1. Background

Skeletal Class III is multifactorial entity consisting of maxillary retrognathism, mandibular prognathism, or a combination thereof. Its treatment often poses a challenge for the orthodontist. Severe skeletal Class III might considerably affect many aspects of the patient's life, including, among others, psychosocial status, esthetics, mastication, speech and even breathing. The latter might be associated with significant differences in the morphological characteristics of the oropharyngeal airway of patients with Class III deformity. Data from Cone Beam Computerized Tomography (CBCT) indicate that Class III adults might have greater total oropharyngeal volume, but also greater

constriction areas in the retroglossal and retropalatal compartment of the oropharynx [1]. The most constricted area of the oropharyngeal airway is usually located at the base of the tongue [2]. At the same time, a positive correlation has been reported among tongue volume, pharyngeal airway and Sella-Nasion-B point (SNB) angle, while a negative correlation has been reported between tongue volume and A point-Nasion-B point (ANB) angle [3]. Finally, Class III patients might have higher risk of being mouth breathers than Class I patients (32% and 23%, respectively) [4].

From the available Class III treatment options, orthopedic modification as well as orthognathic surgery might be expected to exert the greatest influence on the anatomy and volume of the airway. Specifically, significantly more orthognathic patients report a perceived improvement in breathing through maxillary advancement (with or without mandibular setback) (95%) than with mandibular setback alone (56%) [5]. Bimaxillary surgery results in greater increases than mandibular setback in the volume of the airway, which are primarily apparent due to an increase in the retropalatal region [6]. For growing Class III patients, orthopedic appliances are sometimes used to protract the maxilla, restrict or redirect mandibular growth, or both, while at the same time, both approaches lead to a mandibular rotation. However, consensus regarding the impact that these therapeutic approaches might have on the airway has not been reached in the literature. Some studies have reported a favorable effect on the dimensions of the airway [7–10], while others have not confirmed such an effect [11,12]. A recent systematic review on the topic [13] reported that maxillary protraction can increase postpalatal and nasopharyngeal airway dimensions in growing skeletal class III subjects with maxillary retrusion. However, that review included studies published only up to 2017, and its conclusions might be influenced by many existing issues like the lack of an a priori protocol [14], incomplete handling of risk of bias within studies according to the latest Cochrane guidelines [15], issues with the data synthesis (improper model selection, double-counting of multiple arms from single studies and a lack of sensitivity analyses) [16], and the lack of a formal assessment of the review's quality of evidence [17]. Finally, that review only assessed the impact of maxillary protraction on airway dimensions and did not include mandibular restriction with chin-cup.

1.2. Objective

The aim of this systematic review was to assess the effect of different orthopedic appliances on the upper airway dimension in growing patients with class III malocclusion. The research question was “can orthopedic treatment of growing Class III patients with facemask or chin-cup modify the upper airway dimensions to a degree greater than what can be attributed to normal growth?”.

2. Materials and Methods

2.1. Protocol and Registration

A review protocol was designed and registered a priori (PROSPERO CRD42020148142), while post hoc changes were transparently reported (Supplementary Material S1). The conduct and reporting of this review is based on the Cochrane Handbook [18] and PRISMA statement [19], respectively.

2.2. Eligibility Criteria

Clinical studies on human pre-adolescent and adolescent patients of any sex or ethnicity with skeletal Class III malocclusion as an indication for orthopedic treatment were included (Supplementary Material S2). No limitations concerning language, publication year, or status were applied. The primary outcome of this review was total dimensions of the upper airways. Secondary outcomes included other dimensions of the separate airway compartments in linear or areal measurements.

2.3. Information Sources and Search

Nine electronic databases were systematically searched without any restrictions for publication date, type, and language from inception up to 4 August 2020 (Supplementary Material S3), while Directory of Open Access Journals, Digital Dissertations, metaRegister of Controlled Trials, World Health Organization, and Google Scholar, as well as the reference lists of eligible articles or existing systematic reviews were manually searched for any additions.

2.4. Study Selection

Two authors (G.H., V.K.) screened the titles and/or abstracts of studies retrieved from the searches to identify articles that potentially met the inclusion criteria, before moving to their full-texts. Any differences between the two reviewers were resolved by discussion with a third author (S.N.P.).

2.5. Data Collection Process and Items

Data collection from the identified reports was conducted using predefined and piloted forms covering: (a) study characteristics (design, clinical setting, country), (b) patient characteristics (age, sex), (c) inclusion criteria / malocclusion characteristics, (d) treatment characteristics (appliance and duration), (e) post-treatment follow-up duration, and (f) outcome assessment. Data were extracted by two authors (G.H., V.K.) with the aforementioned way to resolve discrepancies.

2.6. Risk of Bias of Individual Studies

The risk of bias of included nonrandomized studies was assessed with the ROBINS-I (“Risk Of Bias In Nonrandomized Studies - of Interventions”) [15]. Assessment of the risk of bias within individual studies was likewise independently performed by two authors (G.H., V.K.) with the same approach being applied to resolve discrepancies.

2.7. Data Synthesis and Summary Measures

An effort was made to include all existing trials in the analysis; where data were missing, they were calculated by us (Supplementary Material S1). As duration of orthopedic effects on the airways might be affected by patient anatomy or growth potential, appliance characteristics and patient compliance, a random-effects model was deemed appropriate to calculate the average distribution of true effects [20] with a restricted maximum likelihood variance estimator [21], using Mean differences (MDs) or Standardized Mean Differences (SMDs) and their corresponding 95% confidence intervals (CIs). The produced forest plots were augmented with contours denoting the magnitude of the observed effects to assess heterogeneity, clinical relevance and imprecision [16] (Supplementary Material S1).

The extent and impact of between-study heterogeneity was gauged visually and quantified with τ^2 (absolute heterogeneity) and the I^2 statistic (relative heterogeneity; inconsistency). Inconsistency over 75% was arbitrarily considered as high, but we also considered where the inconsistency was localized on the forest plot and our uncertainty around these estimates [22]. Ninety-five per cent predictive intervals, integral in the correct interpretation of random-effects meta-analyses [23], were estimated for meta-analyses of ≥ 3 trials to incorporate observed heterogeneity and provide a range of possible effects for a future clinical setting.

2.8. Additional Analyses and Risk of Bias Across Studies

Many subgroup and meta-regression analyses were originally planned (Supplementary Material S1), but only some could be performed in the end. Likewise, reporting biases were planned but could not be assessed in this review.

The overall quality of meta-evidence (i.e., the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE)

approach [17] following recent guidance on synthesizing nonrandomized studies [24] and summary of findings tables were constructed using an improved format [25] (Supplementary Material S1).

Robustness of the results was planned to be checked a priori with sensitivity analyses based on (a) baseline similarity of treated-control group in airway measurements, and (b) sample size, while some sensitivity analyses could not be performed (Supplementary Material S1).

All the analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX) by one author (SNP) with an openly provided dataset [26]. All p values were two-sided with $\alpha = 5\%$, except for the test of between-studies or between-subgroups heterogeneity, where α -value was set at 10% [27].

3. Results

3.1. Study Selection

The electronic literature search yielded 849 results, while one study was manually identified (Figure 1). After duplicate removal and screening of titles/abstracts against the predefined eligibility criteria (Supplementary Material S4), the full texts of 104 papers were checked. Eventually, 10 papers pertaining to 9 unique studies (1 prospective and 9 retrospective nonrandomized studies; Table 1), which were published as journal papers, were finally included [8,11,12,28–34].

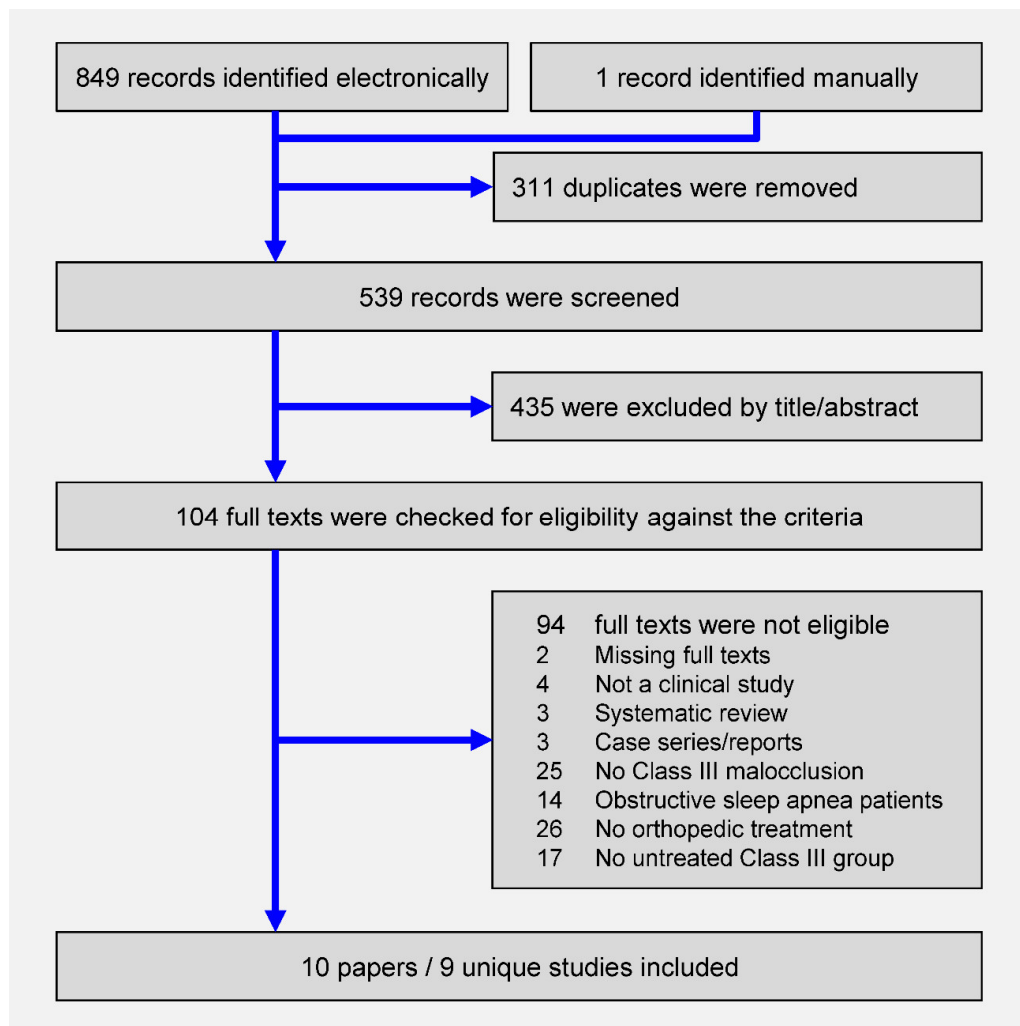


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the identification and selection of studies.

3.2. Study Characteristics

All primary studies were conducted in university clinics ($n = 9$; 100%) and originated from four different countries (Iran, Italy, Spain, Turkey) (Table 1). A total of 321 treated and 145 untreated Class III patients were included, with a median total sample of 45 patients per included study (range 34 to 78 patients per study). All studies reported patient sex and age, with 199 of 466 patients (42.7%) being male and the mean patient age being 9.1 years.

Table 1. Characteristics of the included studies.

Study	Design; Setting; Country *	Patients (M/F); Age †	Inclusion Criteria	Appliance (Active Duration)	FU	Imaging Modality
Akin [28]	rNRS; Uni; TR	EG1: 25 (10/15); 10.3 EG2: 25 (9/16); 9.8 CG: 17 (8/9); 10.1	EG1-2/CG: $-5^{\circ} \leq \text{ANB} \leq 0^{\circ}$; Cl. III MoRel; edge-to-edge or aCB InRel; flat / mildly concave profile; successful Tx	EG1: FM + RME (NR) EG2: CC (NR) CG: (6.0 mos)	-	LC
Tuncer [9]	rNRS; Uni; TR	EG: 20 (10/10); 10.3 CG: 18 (10/8); 9.9	EG/CG: mandibular prognathism without shift; neutral SN-ML	EG: CC + BP (9.8 mos) CG: (11.1)	-	LC
Tuncer [29]	rNRS; Uni; TR	EG1: 17 (9/8); 11.3 EG2: 17 (10/7); 11.5 CG: 11(8/3); 9.1	EG1-2/CG: $\text{ANB} < 0^{\circ}$; $\text{SNA} < 82^{\circ}$; aCB InRel; HWR between PP2 and MP3cap; neutral (EG1)/high SN-ML (EG2);	EG1: FM + BP (9.7 mos) EG2: FM + BP (10.6 mos) CG: (12.0 mos)	-	LC
Danaei [30]	rNRS; Uni; IR	EG: 19 (6/13); 7.9 CG: 15 (4/11); 7.5	EG/CG: $\text{SNA} < 77^{\circ}$, $76^{\circ} \leq \text{SNB} \leq 80^{\circ}$, $\text{ANB} < 1^{\circ}$; aCB InRel; Cl. III MoRel; no shift	EG: FM (10.5 mos) CG: (10.5 mos)	-	LC
Kilinc [31]	rNRS; Uni; TR	EG: 18 (7/11); 10.5 CG: 17 (8/9); 10.9	EG/CG: maxillary skeletal retrusion; aCB InRel; Cl. III MoRel; HWR between PP2 and MP3cap	EG: FM + RME (6.9 mos) CG: (9.8 mos)	-	LC
Lombardo [32]	rNRS; Uni; IT	EG: 47 (22/25); 7.8 CG: 18 (9/9); 8.9	EG/CG: edge-to-edge or aCB InRel; Cl. III MoRel; WITS ≤ -2 mm; no shift; CVM stage 1–3	EG: FM + RME + BP (24.0 mos) CG: (25.2 mos)	5.4 yrs	LC
Menendez-Diaz [33]	rNRS; Uni; ES	EG: 64 (10/34); 8.1 CG: 14 (8/6); 8.2	EG/CG: Cl. III; no shift	EG: FM + RME (18.0 mos) CG: (23.2 mos)	-	LC
Mucedero [11]; Baccetti [12]	rNRS; Uni; IT	EG1: 22 (10/12); 8.9 EG2: 17 (10/7); 7.1 CG: 20 (8/12); 8.1	EG1-2/CG: WITS ≤ -2 mm; edge-to-edge or aCB InRel; Cl. III MoRel	EG1: FM + BP (19.2 mos) EG2: FM + RME (25.2 mos) CG: (22.8 mos)	2.1 yrs	LC
Yagci [34]	pNRS; Uni; TR	EG1: 15 (7/8); 9.6 EG2: 15 (8/7); 9.5 CG: 15 (8/7); 9.8	EG/CG: Cl. III MoRel; edge-to-edge or aCB InRel; $\text{ANB} \leq 0^{\circ}$; N-Aperp ≤ -2 mm	EG1: FM1 + RME (13.4 mos) EG2: FM2 + RME (14.9 mos) CG: (11.64)	-	LC

* given with the country's ISO 3166 alpha-2 code. † given as mean (one value) or if mean not reported given as range (two values in parenthesis). aCB, anterior cross bite; ANB, A point-Nasion-B point angle; BP, Bite plane or bite block; CC, chin cup; CG, control group; Cl., Angle's Class; CVM, cervical vertebrae maturation index; EG, experimental group; FM, facemask or other maxillary protraction appliance; HWR, hand-wrist radiograph; InRel, incisor relationship; LC, lateral ceph; mo, month; MoRel, molar relationship; MP3, middle phalanx of the third finger; NR, not reported; pNRS; prospective nonrandomized study; PP2, proximal phalanx of the second finger; RME, rapid maxillary expansion; rNRS, retrospective nonrandomized study; SNA, Sella-Nasion-A point angle; SNB, Sella-Nasion-B point angle; SN-ML, Sella-Nasion-mandibular plane angle; Tx, treatment; Uni, university clinic; yr, year.

Seven of the included studies assessed maxillary protraction with facemask / reverse headgear, one assessed mandibular restraint with chin-cup, and one included one facemask arm and one chin-cup arm. Among the eight facemask studies, four incorporated maxillary expansion, two included a bite-plane (or bite-blocks) and one included both maxillary expansion and bite-plane. Average treatment duration was 15.1 months for facemask treatment (7 studies; range 6.9 to 24.0 months) and 9.8 months for chin-cup (1 study), while the average observation period for the untreated controls was 14.7 months (9 studies; 6.0 to 25.2 months). All studies measured outcomes before and directly after treatment, while two studies additionally remeasured outcomes postretention after an additional average period of 2.1 to 5.1 years. Finally, all studies assessed the effects of treatment on airways with lateral cephalograms.

3.3. Risk of Bias within Studies

The included nonrandomized trials presented several issues influencing their risk for bias (Table 2). All studies except one ($n = 8$; 89%) were retrospective, and patient selection could influence the results of treatment for most of them ($n = 8$; 89%). For at least three studies (33%), treated/control patients were followed/observed for different durations, while baseline differences in age, sex, malocclusion severity or airway measurements existed for 1–3 studies (11–33%). No study performed blinded outcome measurement, while for at least four studies (44%), the treated and control populations originated from different sources. All included studies were judged to be in critical risk of bias, as issues existed for at least three domains per study.

3.4. Results of Individual Studies and Data Synthesis

3.4.1. Maxillary Protraction with Facemask/Reverse Headgear

Eight studies provided various measurements of linear distances or area measurements of airways post-treatment or postretention. The results of the performed meta-analyses are given in Table 3, while the results of single studies that could not be pooled in meta-analyses are given in Supplementary Material S5.

Table 2. Detailed assessment of included nonrandomized studies with the ROBINS-I tool.

Reference	Akin [28]	Tuncer [9]	Tuncer [29]	Danaei [30]	Kilinc [31]	Lombardo [32]	Menendez-Diaz [33]	Mucedero [11]; Baccetti [12]	Yagci [34]
Was the study prospective?	N	N	N	N	N	N	N	N	Y
Was selection of patients based on any factor that could influence airways post treatment (age, sex, skeletal configuration, compliance, breakages)?	Y	PY	Y	Y	PY	PN	PY	PY	Y
Were treated/untreated groups clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the observation period similar for treated/untreated patients?	NI	Y	PN	PY	PN	Y	PN	PN	PY
Were treated/untreated patients similar in terms of baseline age?	Y	PY	PN	Y	Y	PY	Y	PY	Y
Were treated/untreated patients similar in terms of baseline sex?	Y	PY	PN	Y	N	PY	N	N	Y
Were treated/untreated patients similar in terms of dental/skeletal malocclusion?	Y	PY	N	NI	Y	PY	Y	Y	Y
Were treated/untreated patients similar in terms of baseline airways?	PN	PN	Y	Y	Y	PY	Y	Y	N
Was the use of any other appliances/adjuncts the same among treated/untreated patients?	NA	NA	NI	NI	NA	NA	NI	NA	NA
Was outcome measurement similar for treated/untreated patients?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was outcome measurement done blindly for both treated/untreated patients?	N	N	N	N	N	N	N	N	N
Were treated/untreated patients treated/observed at the same place/time?	NI	NI	N	NI	N	N	N	N	Y

N, no; NA, not applicable; NI, no information; PN, probably not; PY, probably yes; Y, yes.

Table 3. Random-effects meta-analyses on the effect of facemask (with / without maxillary expansion) on upper airway dimensions.

Outcome	<i>n</i>	Effect (95% CI)	<i>p</i>	I ² (95% CI)	tau ² (95% CI)	95% prediction
<i>Post-treatment</i>						
Total nasopharyngeal area (mm ²)	4	SMD = 1.62 (1.20, 2.04)	<0.001	23% (0%, 91%)	0.04 (0, 1.42)	0.34, 2.90
Adenoidal nasopharyngeal area (mm ²)	2	MD = 0.34 (−0.10, 0.77)	0.13	0% (0%, 99%)	0 (0, 7.60)	-
Aerial nasopharyngeal area (mm ²)	2	MD = 1.29 (0.80, 1.77)	<0.001	0% (0%, 99%)	0 (0, 14.38)	-
Oropharyngeal area (mm ²)	2	MD = −0.18 (−1.65, 1.29)	0.81	89% (24%, 100%)	1.00 (0.04, 141.23)	-
Upper adenoid size (AD2-H; mm)	3	MD = 0.59 (−0.52, 1.70)	0.30	57% (0%, 98%)	0.55 (0, 24.22)	−11.24, 12.42
Lower adenoid size (AD1-Ba; mm)	3	MD = 0.12 (−2.20, 2.44)	0.92	76% (0%, 99%)	3.11 (0, 76.33)	−26.88, 27.12
Upper airway dimension (PNS-AD2; mm)	6	MD = 2.45 (0.97, 3.92)	0.001	87% (64%, 97%)	2.83 (0.74, 15.17)	−2.67, 7.57
Lower airway dimension (PNS-AD1; mm)	6	MD = 2.10 (1.50, 2.70)	<0.001	5% (0%, 87%)	0.04 (0, 4.83)	1.11, 3.09
McNamara's upper pharynx dimension (mm)	6	MD = 1.59 (0.57, 2.62)	0.002	73% (15%, 95%)	1.08 (0.07, 7.56)	−1.63, 4.82
McNamara's lower pharynx dimension (mm)	6	MD = 1.02 (0.17, 1.88)	0.02	70% (16%, 94%)	0.69 (0.06, 4.90)	−1.58, 3.63
<i>Postretention</i>						
Upper adenoid size (AD2-H; mm)	2	MD = −1.13 (−4.25, 2.00)	0.48	72% (0%, 100%)	3.70 (0, 641.91)	-
Lower adenoid size (AD1-Ba; mm)	2	MD = −2.67 (−4.63, −0.70)	0.008	14% (0%, 99%)	0.31 (0, 275.16)	-
Upper airway dimension (PNS-AD2; mm)	2	MD = 3.71 (0.80, 6.62)	0.01	65% (0%, 100%)	2.91 (0, 563.83)	-
Lower airway dimension (PNS-AD1; mm)	2	MD = 3.59 (1.75, 5.44)	<0.001	0% (0%, 98%)	0 (0, 132.16)	-
McNamara's upper pharynx dimension (mm)	2	MD = 2.27 (0.80, 3.74)	0.003	0% (0%, 98%)	0 (0, 89.15)	-
McNamara's lower pharynx dimension (mm)	2	MD = 1.84 (−2.08, 5.75)	0.36	85% (NC)	6.80 (NC)	-

CI, confidence interval; MD, mean difference; SMD, standardized mean difference. Statistical significance is denoted in bold.

The review's primary outcome of total airway area was assessed by a single study, which found a statistically and clinically relevant increase in airway area post-treatment (MD = 222.86 mm²; 95% CI = 14.04–431.68 mm²; $p = 0.04$). As far as secondary outcomes, statistically significant post-treatment increases were seen for the facemask group compared to the control group regarding total nasopharyngeal area (4 studies; SMD = 1.62; 95% CI = 1.20–2.04; $p < 0.001$; $I^2 = 23\%$; Supplementary Material S6), arial nasopharyngeal area (2 studies; MD = 1.29 mm²; 95% CI = 0.80–1.77 mm²; $p < 0.001$; $I^2 = 0\%$), upper airway dimensions (6 studies; MD = 2.45 mm; 95% CI = 0.97–3.92 mm; $p = 0.001$; $I^2 = 87\%$; Supplementary Material S7), lower airway dimensions (6 studies; MD = 2.10 mm; 95% CI = 1.50–2.70 mm; $p < 0.001$; $I^2 = 5\%$; Supplementary Material S8), McNamara's upper pharynx dimensions (6 studies; MD = 1.59 mm; 95% CI = 0.57–2.62 mm; $p = 0.002$; $I^2 = 73\%$; Supplementary Material S9), and McNamara's lower pharynx dimensions (6 studies; MD = 1.02 mm; 95% CI = 0.17–1.88 mm; $p = 0.02$; $I^2 = 70\%$; Supplementary Material S10). Observed heterogeneity was acceptable in all instances, except for the meta-analysis of upper airway dimensions ($I^2 = 87\%$), but all studies were on the right side of the forest plot (Supplementary Material S7), so judgment about the beneficial effects of treatment was not influenced by it, but rather, only the precise quantification of the treatment's effects. The 95% prediction intervals were inconsistent (included both negative and negative values) for most meta-analyses, with only total pharyngeal area and lower airway dimension being consistent, meaning that we can consistently expect significant benefits in every future scenario.

Apart from these meta-analyses, individual studies reported on several increases in airway dimensions (Supplementary Material S5) that were either statistically nonsignificant or clinically nonrelevant, apart from a relevant increase in oropharynx dimensions.

Finally, postretention data 2.1 to 5.4 years after treatment were available from two studies (Table 3). Lower adenoid side was significantly lower in treated patients compared to controls (2 studies; MD = −2.67 mm; 95% CI = −4.63 – −0.70 mm; $p = 0.008$), a novel finding that was not seen directly post-treatment. The dimensions of the upper and lower airways were still significantly larger among treated than untreated patients and to a greater extent than directly post-treatment (MD of 3.71 mm versus 2.45 mm for the upper airway; MD of 3.59 mm versus 2.10 mm for the lower airway). Treatment-related benefits in the dimensions of the pharynx were likewise increased postretention, though this increase was statistically significant only for the upper pharynx.

3.4.2. Mandibular Restraint with Chin-Cup

Two studies provided various measurement on linear distances or area measurements of airways post-treatment (Supplementary Material S11), most of which were not significant—with two exceptions. One study reported a post-treatment increase of the nasopharyngeal area (MD = 10183.0 mm²; 95% CI = 10074.3–10291.8 mm²; $p < 0.001$), which was both statistically significant and clinically relevant. The same study reported a post-treatment reduction of the oropharyngeal area (MD = −8231.0 mm²; 95% CI = −10616.5 – −5845.5 mm²; $p < 0.001$), which was statistically significant but clinically irrelevant.

3.5. Additional Analyses, Risk of Bias across Studies, and Quality of Evidence

Several subgroup analyses, meta-regressions and assessments for reporting biases were originally planned in the protocol, but could ultimately not be performed (Supplementary Material S1). Selected subgroup and meta-regression analyses on the post-treatment effects of maxillary protraction (for meta-analyses with ≥ 5 studies) found no significant influence of patient age, sex, baseline airway dimensions, inclusion of maxillary expansion or treatment duration (Table 4). Likewise, one study found no significant differences between normodivergent or hyperdivergent patients, and another study found no significant differences between two facemask designs.

Table 4. *p* values from subgroup analyses and meta-regressions.

Outcome	Age	Male%	Baseline Airway	RME	Tx Duration
Upper airway dimension (PNS-AD2; mm)	0.45	0.65	0.69	0.29	0.27
Lower airway dimension (PNS-AD1; mm)	0.98	0.15	0.37	0.65	0.26
McNamara's upper pharynx dimension (mm)	0.46	0.23	0.46	0.81	0.33
McNamara's lower pharynx dimension (mm)	0.13	0.65	0.45	0.70	0.67

RME, rapid maxillary expansion, Tx, treatment.

The quality of evidence (Table 5) for the main analyses on the post-treatment effects of facemask was, in all cases, very low, due to the inclusion of retrospective nonrandomized studies with critical risk of bias. The quality of evidence about the primary outcome of total airway area was additionally downgraded due to imprecision, as a single study with a limited sample size contributed to this. The GRADE analysis indicates that further research in terms of well-designed studies is very likely to have an important impact which will likely change our current estimates of effect.

Table 5. Summary of Findings Table according to GRADE approach.

Outcome Studies (patients)	Anticipated Absolute Effects (95% CI)		Quality of the evidence (GRADE) ^b	What happens with maxillary protraction
	Control (growth)	Maxillary protraction		
Total airway area 35 patients (1 study)	−38.4 mm ²	223 mm ² greater (14.0 to 431.7 mm ² greater)	○○○○ very low ^{c,d} due to bias, imprecision	Might be associated with greater airway area
Upper airway dimensions 316 patients (6 studies)	0.3 mm ^a	2.5 mm greater (1.0 to 3.9 mm greater)	○○○○ very low ^c due to bias	Might be associated with greater upper airway dimensions
Lower airway dimensions 316 patients (6 studies)	0.5 mm ^a	2.1 mm greater (1.5 to 2.7 mm greater)	○○○○ very low ^c due to bias	Might be associated with greater lower airway dimensions
Upper pharynx dimensions (McNamara's) 323 patients (6 studies)	0.6 mm ^a	1.6 mm greater (0.6 to 2.6 mm greater)	○○○○ very low ^c due to bias	Might be associated with greater upper pharynx dimensions
Lower pharynx dimensions (McNamara's) 323 patients (6 studies)	0.1 mm ^a	1.0 mm greater (0.2 to 13.9 mm greater)	○○○○ very low ^c due to bias	Might be associated with greater lower pharynx dimensions

Intervention: orthopedic maxillary protraction with facemask or reverse headgear/Population: pre-adolescent children with skeletal Class III malocclusion / Setting: university clinics (Iran, Italy, Spain, Turkey). ^a Response in the control group is based on random-effects meta-analysis of the control groups of included studies. ^b Starts from “high”. ^c Downgraded by three levels for bias due to the inclusion of retrospective nonrandomized studies with serious risk of bias. ^d Downgraded by one level for imprecision due to the inclusion of an inadequate sample. CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation, ○○○○, downgraded by 4 points.

3.6. Sensitivity Analysis

A sensitivity analysis according to sample size and baseline similarity of treated/control patients (Supplementary Material S12) indicated relative robustness of the results.

4. Discussion

4.1. Evidence in Context

The current review summarizes and critically appraises existing evidence from clinical research comparing the effects of Class III orthopedic treatment on airway dimensions to untreated Class III controls. A total of 10 papers (9 studies) including 321 treated and 145 untreated Class III patients were finally identified as eligible and contributed to data synthesis.

Maxillary protraction with a facemask, with or without an expander, was shown to result in statistically significant increases in airway dimensions directly after treatment compared to what could be expected by Class III growth alone. Specifically, benefits were seen for total nasopharyngeal area, upper/lower airway dimensions and upper/lower pharynx dimensions (Table 3). However, most of these changes were small to moderate in magnitude, which means that they might have little clinical relevance (Supplementary Materials S7–S10). The only exception was the increase in total nasopharyngeal area, where a large to very large effect was (Supplementary Material S6) found. This indicates that any clinically relevant benefits in airway dimensions or breathing might be located in this compartment. Evidence from the existing literature indicates that significant differences exist in the dimensions of the pharyngeal airway and the thickness of the pharyngeal wall among normal patients and patients with sleep-disordered breathing [35], with the lower retropalatal and retroglossal areas being affected the most [36]. Even though these regions were only minimally affected, the large improvements at the nasopharyngeal area might be highly relevant, since the nasopharyngeal dimensions appear to be the most sensitive parameter for assessments of the patient's respiratory conditions [37]. However, even though dimensional changes might be indicative of improved breathing, proper confirmation must follow using functional analyses of nasal airflow resistance and nasal pressure.

The initial effects on the airways observed after treatment were, for the most part, retained after a follow-up period of 2–5 years, while in some instances, the difference between treated and untreated Class III patients even increased (Table 3). This might indicate that early orthopedic modification of a maxillary retrusion might be associated with a more favorable growth pattern, even though this is speculative at the present time. A long-term follow-up from a well-known randomized trial on maxillary protraction indicated relatively similar change patterns for SNA, SNB and ANB angles from 8 to 14 years of age for treated and untreated Class III patients, with mandibular rotation being the most pronounced difference [38]. Different extents of mandibular rotation, as expressed through the patient's growth pattern, were observed to be differently related to airway dimensions in Class I patients [39]. Apart from that, therapeutic effects should always be considered in the context of physiological growth. The dimensions of the nasopharyngeal compartment are not stable during growth [40,41], and patient age at the time of the investigation could play a role in the interpretation of the results.

The effects of orthopedic maxillary traction on the airways were relatively consistent, despite the big variability of the included studies regarding patient characteristics (age, sex, baseline airway dimensions) and treatment protocol (simultaneous use of maxillary expansion or treatment duration), as no clear modification was seen through the subgroup/meta-regression analyses (Table 4). Previous studies have indicated that maxillary expansion can have a beneficial effect on upper airway dimensions [42], but whether additional gains can be expected during maxillary protraction by also incorporating expansion remains questionable. It must be also noted here that alternating rapid maxillary expansion and constriction might be more beneficial than conventional rapid maxillary expansion in terms of skeletal effects [43], but no included studies used this protocol.

Restricting or redirecting mandibular growth with a chin-cup had a considerably smaller impact on the airways than maxillary protraction, since only two statistically significant differences directly post-treatment were found, and only one was clinically relevant (the increase in nasopharyngeal area) (Supplementary Material S11). However, it must be noted that only two small studies were included in this review, which might indicate an absence of evidence, and not necessarily evidence of absence. Chin-cup treatment has been reported to induce certain skeletal adaptations [44,45], the long-term stability of which, however, is questionable. At the present time, there is not enough evidence to suggest that chin-cup treatment negatively influences airway dimensions.

4.2. Strengths and Limitations

This systematic review has several strengths, comprising an a priori registered protocol [14], a comprehensive literature search, the inclusion of an untreated Class III control group, the use of modern analytic methods [21], the application of the GRADE approach to assess the strength of provided recommendations [17], and the transparent provision of all data [46].

Some limitations exist nonetheless. For one, methodological issues, which might influence the present conclusions, existed in all the included studies. This is especially the case in the included retrospective nonrandomized studies [47,48]. The inclusion of nonrandomized studies in meta-analyses is not considered prohibitory per se, provided that robust bias appraisal has been performed and recent guidance has been provided on how to appropriately incorporate such designs [24]. Furthermore, most meta-analyses were predominantly based on small trials, which might affect the precision of the estimates [49]. Additionally, the small number of trials ultimately included in the meta-analyses and their incomplete reporting of results and potential confounders (baseline malocclusion severity or other patient characteristics and different orthopedic treatment protocols) prevented us from conducting many analyses for subgroups and meta-regressions. Last but not least, this study, although it was originally otherwise planned, only included lateral cephalograms for evaluating airway dimensions because no eligible controlled study with CBCTs could be found. Lateral cephalograms are abundantly available because they are part of patients' usual records, but only a moderately high correlation is to be expected between cephalometric and CBCT measurements in the assessment of the airway dimensions [50].

5. Conclusions

Current evidence indicates that orthopedic treatment with maxillary protraction for Class III malocclusion might be associated with increased dimensions of the upper airways, which seem to be retained after treatment. However, our confidence in these data is very low due to the poor quality of existing studies and their small number. Restriction of mandibular growth with chin-cup seems likewise to be associated to some extent with increased airway dimensions, but these effects are less pronounced. It is crucial that the clinical relevance of such anatomical changes be confirmed by functional analyses of breathing ability before concrete recommendations can be formulated.

Supplementary Materials: The following are available online at www.mdpi.com/2077-0383/9/9/3015/s1, Supplementary Material S1: Additional review details and deviations from the protocol, Supplementary Material S2: Eligibility criteria for the inclusion of primary studies, Supplementary Material S3: Literature search (as of 4 August 2020) for each database with the corresponding hits, Supplementary Material S4: List of studies identified from the literature search and their inclusion/exclusion status with reasons, Supplementary Material S5: Results of individual studies comparing maxillary protraction to untreated controls that are not included in meta-analyses, Supplementary Material S6: Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of total nasopharyngeal area, Supplementary Material S7: Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of upper airway dimension, Supplementary Material S8: Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of lower airway dimension, Supplementary Material S9: Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of McNamara's upper pharynx dimension, Supplementary Material S10: Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of

McNamara's lower pharynx dimension, Supplementary Material S11: Results of individual studies comparing chin-cup to untreated controls that are not included in meta-analyses, Supplementary Material S12: Sensitivity analyses of meta-analyses post-treatment with at least 3 studies.

Author Contributions: G.H. wrote the first draft of the protocol, while V.K., T.E., and S.N.P. revised it. G.H. and S.N.P. did the literature searches. G.H. and V.K. independently performed study selection in duplicate, data extraction, and risk of bias assessment. Disagreements were resolved with two authors S.N.P. and T.E.. Literature searches and data analysis were performed by the last author (S.N.P.). G.H. wrote the first draft of the manuscript, while V.K., T.E., and S.N.P. revised it. All authors have read and agreed to the published version of the manuscript.

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Supplementary Materials

Supplementary Material S1. Additional review details and deviations from the protocol.

Deviations from the protocol
The SMD was decided post hoc to be used post-hoc to pool 4 studies with slightly different cephalometric measurements of total nasopharyngeal area.
Several factors were planned to be assessed through subgroup analyses/meta-regressions in meta-analyses of at least 5 studies, but they could not be ultimately conducted due to limited material/reporting: (i) subsets according to the patient characteristics (patient skeletal age, ethnicity, craniofacial configuration, masticatory activity, etc.), (ii) subsets according to variations of administered treatment and any co-interventions like use of extraoral appliances, skeletal anchorage, full fixed appliances, etc, (iii) subsets according to patient compliance with the treatment.
Robustness of the results was planned a priori to be checked a priori with sensitivity analyses based on (a) inclusion/exclusion of non-randomized studies, (b) inclusion/exclusion of trials with methodological shortcomings, and (c) improvement of the GRADE classification. No such sensitivity analyses could be performed.
Additional methods
Forest plots were augmented with contours denoting effect size for orthopedic treatment, according to the average Standard Deviation (SD) pre-treatment of the untreated control group: <ul style="list-style-type: none">▪ Small (up to half SD)▪ Moderate (half to one SD)▪ Large (one to two SDs)▪ Very large (over two SDs)
The minimal clinically important, large, and very large effects for the GRADE approach were defined as half, one, and two standard deviations of the response of the control (underage) group (Norman et al., 2003).
References
Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. <i>Med Care</i> . 2003;41:582–92.

Supplementary Material S2. Eligibility criteria for the inclusion of primary studies.

	Inclusion criteria	Exclusion criteria
Patients	Patients of any age, gender, or ethnicity with Class III malocclusion due to a retrusive maxilla, protrusive mandible, or a combination of both scheduled to research orthopedic treatment	Patients with congenital malformations, clefts, any other syndromes, or obstructive sleep apnea
Intervention	Any kind of orthopedic treatment for Class III with facemask / reverse headgear or chin-cup	Any other kind of intervention
Control	Growing patients with skeletal Class III malocclusion without treatment	Untreated patients without Class III malocclusion
Outcome	Airway dimensions	-
Studies	Randomized and prospective / retrospective non-randomized controlled clinical trials	Animal studies, case reports/series, non-clinical studies, and cross-sectional studies

Supplementary Material S3. Literature search (as of August 4th, 2020) for each database with the corresponding hits.

Nr	Database	Search	Limits	
1	MEDLINE (through PubMed)	((("Class III" OR "Cl. III" NOT "Class II" OR ((maxill* OR upper) AND retrognath*) OR ((mandib* OR lower) AND prognath*) OR (anter* AND (crossbite* OR "cross-bite" OR "cross-bites")))) AND (((orthop* OR orthodon* OR functional) AND (treatment* OR therap* OR appliance*)) OR facemask* OR Delaire OR "reverse headgear" OR "reverse Activator" OR chincup OR "chin-cup") AND (airway* OR ((pharyn* OR oropharyn* OR nasopharyn* OR hypopharyn*) AND (volume OR area OR cephalomet*))))))		253
3	CDSR	Same as MEDLINE		1
4	CENTRAL	Same as MEDLINE		34
5	DARE	Same as MEDLINE		0
6	Embase	Same as MEDLINE		120
7	Scopus	(TITLE-ABS-KEY (("Class III" OR "Cl. III" OR ((maxill* OR upper) AND retrognath*) OR ((mandib* OR lower) AND prognath*) OR (anter* AND (crossbite* OR "cross-bite" OR "cross-bites")))) AND TITLE-ABS-KEY (((orthop* OR orthodon* OR functional) AND (treatment* OR therap* OR appliance*)) OR facemask* OR delaire OR "reverse headgear" OR "reverse Activator" OR chincup OR "chin-cup")) AND TITLE-ABS-KEY ((airway* OR ((pharyn* OR oropharyn* OR nasopharyn* OR hypopharyn*) AND (volume OR area OR cephalomet*)))))	Dentistry	125
8	WOK	Same as MEDLINE	Dentistry, oral surgery, medicine	200
9	VHL	Same as MEDLINE		116
Sum (with overlaps)				849
Sum (without overlaps)				539

CDSR, Cochrane Database of Systematic Reviews; DARE, Cochrane Database of Abstracts of Reviews of Effects; CENTRAL, Cochrane Central Register of Controlled Trials; VHL, virtual health library; WOK, Web of Knowledge.

Supplementary Material S4. List of studies identified from the literature search and their inclusion/exclusion status with reasons.

Nr	Paper	Status
1	[No authors] [Lung transplantation in emphysema]. <i>Medicina (B Aires)</i> . 1997;57(5):521-9.	Excluded by title
2	{IRCT138903033915N} Hemodynamic responses to intubation in hypertensive patients. http://www.who.int/trialssearch/trial2.aspx?Trialid=irct138903033915n2 . 2011.	Excluded by title
3	{IRCT201108167346N} Effect of continuous positive airway pressure in the treatment of refractory hypertension in patients with severe obstructive sleep apnea. http://www.who.int/trialssearch/trial2.aspx?Trialid=irct201108167346n1 . 2011.	Excluded by title
4	{NCT} Comparison of Treatment Effects of PowerScope2 and Forsus Using CBCT. https://clinicaltrials.gov/show/nct03296644 . 2017.	Excluded by title
5	Abdelrahman TE, Takahashi K, Tamura K, Nakao K, Hassanein KM, Alsuity A, et al. Impact of different surgery modalities to correct class III jaw deformities on the pharyngeal airway space. <i>J Craniofac Surg</i> . 2011;22(5):1598-601.	Excluded by title
6	Abreu MFFd. Análise dos aspectos biomédicos gerais e bucais em pacientes com doença de Alzheimer. 2019. p. 68-.	Excluded by title
7	Acevedo Pérez JL, Sánchez López A, Núñez Núñez C. Logopedia en paciente con mapeo cortical intraoperatorio. <i>Rev logop foniatr audiol (Ed impr)</i> . 2017;37(1):43-9.	Excluded by title
8	Adams HR, Defendorf S, Vierhile A, Mink JW, Marshall FJ, Augustine EF. A novel, hybrid, single- and multi-site clinical trial design for CLN3 disease, an ultra-rare lysosomal storage disorder. <i>Clinical trials (London, England)</i> . 2019;16(5):555-60.	Excluded by title
9	Adolfo JR, Dhein W, Sbruzzi G. Intensity of physical exercise and its effect on functional capacity in COPD: systematic review and meta-analysis. <i>J bras pneumol</i> . 2019;45(6):e20180011-e.	Excluded by title
10	Akarsu-Guven B, Karakaya J, Ozgur F, Aksu M. Growth-related changes of skeletal and upper-airway features in bilateral cleft lip and palate patients. <i>Am J Orthod Dentofacial Orthop</i> . 2015;148(4):576-86.	Excluded by title
11	Albino CC, Graf H, Paz-Filho G, Diehl LA, Olandoski M, Sabbag A, et al. Radioiodine plus recombinant human thyrotropin do not cause acute airway compression and are effective in reducing multinodular goiter. <i>Braz j med biol res</i> . 2010;43(3):303-9.	Excluded by title
12	Alcalde J, Pastor MJ, Quesada JL, Martín E, García Tapia R. Reconstrucción de defectos orofaríngeos con colgajo lateral de brazo. <i>Acta otorinolaringol esp</i> . 2001;52(1):39-44.	Excluded by title
13	Al-Dohan AM, Al-Jewair TS. Limited Evidence Suggests That Presurgical Orthodontics May Not Be Needed for Orthognathic Surgery Patients. <i>Journal of Evidence-Based Dental Practice</i> . 2017;17(1):39-41.	Excluded by title
14	Alfwaress F, Al Maaitah E, Al-Khateeb S, Abu Zama Z. The relationship of vocal tract dimensions and substitution of the palatal approximant /j/ for the alveolar trill /r/. <i>International Journal of Speech-Language Pathology</i> . 2015;17(5):518-26.	Excluded by title
15	Alkawari HM, Albalbesi HO, Alhendy AA, Alhuwaish HA, Al Jobair AA, Baidas L. Pharyngeal airway dimensional changes after premolar extraction in skeletal class II and class III orthodontic patients. <i>Journal of Orthodontic Science</i> . 2018;7(1).	Excluded by title
16	Allareddy V, Ching N, Macklin EA, Voelz L, Weintraub G, Davidson E, et al. Craniofacial features as assessed by lateral cephalometric measurements in children with Down syndrome. <i>Prog Orthod</i> . 2016;17(1):35.	Excluded by title
17	Almeida RCC, Artese F, Carvalho FdAR, Cunha RD, Almeida MAdO. Comparação entre a radiografia de cavum e a cefalométrica de perfil na avaliação da nasofaringe e das adenoides por otorinolaringologistas. <i>Dental press j orthod (Impr)</i> . 2011;16(1):e1-e10.	Excluded by title
18	Al-Moraissi EA, Al-Magaleh SM, Iskandar RA, Al-Hendi EA. Impact on the pharyngeal airway space of different orthognathic procedures for the prognathic mandible. <i>Int J Oral Maxillofac Surg</i> . 2015;44(9):1110-8.	Excluded by title
19	Almuzian M, Almukhtar A, Ju X, Al-Hiyali A, Benington P, Ayoub A. Effects of Le Fort I Osteotomy on the Nasopharyngeal Airway-6-Month Follow-Up. <i>J Oral Maxillofac Surg</i> . 2016;74(2):380-91.	Excluded by title
20	Alonso-Rodríguez E, Gomez E, Martin M, Munoz JM, Hernandez-Godoy J, Burgueno M. Beckwith-Wiedemann Syndrome: Open bite evolution after tongue reduction. <i>Med Oral Patol Oral Cir Bucal</i> . 2018;23(2):e225-e9.	Excluded by title
21	Alves RdSA, Vianna FdAF, Pereira CAAdC. Fenótipos clínicos de asma grave. <i>J bras pneumol</i> . 2008;34(9):646-53.	Excluded by title
22	Amini F, Borzabadi-Farahani A, Behnam-Roudsari G, Jafari A, Shahidinejad F. Assessment of the uvulo-glossopharyngeal dimensions in patients with beta-thalassemia major. <i>Sleep Breath</i> . 2013;17(3):943-9.	Excluded by title
23	Ancochea J, Gómez García T, Miguel Díez Jd. Hacia un tratamiento individualizado e integrado del paciente con EPOC. <i>Arch bronconeumol (Ed impr)</i> . 2010;46(supl.10):14-8.	Excluded by title
24	Andrade CRd, Chatkin JM, Camargos PAM. Avaliação do grau de controle clínico, espirométrico e da intensidade do processo inflamatório na asma. <i>J pediatr (Rio J)</i> . 2010;86(2):93-100.	Excluded by title
25	Andrea R, Lopez-Giraldo A, Falces C, Sobradillo P, Sanchis L, Gistau C, et al. Lung function abnormalities are highly frequent in patients with heart failure and preserved ejection fraction. <i>Heart Lung Circ</i> . 2014;23(3):273-9.	Excluded by title
26	Ankichev S, Chung F. Considerations for patients with obstructive sleep apnea undergoing ambulatory surgery. <i>Current Opinion in Anaesthesiology</i> . 2011;24(6):605-11.	Excluded by title
27	Annoni R, Silva WR, Mariano MdS. Análise de parâmetros funcionais pulmonares e da qualidade de vida na revascularização do miocárdio. <i>Fisioter mov</i> . 2013;26(3):525-36.	Excluded by title
28	Antonia Rodríguez M, Friedberg JP, DiGiovanni A, Binhuan W, Wylie-Rosett J, Sangmin H, et al. A Tailored Behavioral Intervention to Promote Adherence to the DASH Diet. <i>American journal of health behavior</i> . 2019;43(4):659-70.	Excluded by title
29	Araújo CFdSnd, Braga PlDs, Ferreira JdB. Tratamento tardio de fratura condilar: Relato de caso. <i>Rev cir traumatol buco-maxilo-fac</i> . 2013;13(3):17-24.	Excluded by title
30	Athanasios AE, Toutountzakis N, Mavreas D, Ritzau M, Wenzel A. Alterations of hyoid bone position and pharyngeal depth and their relationship after surgical correction of mandibular prognathism. <i>Am J Orthod Dentofacial Orthop</i> . 1991;100(3):259-65.	Excluded by title
31	Avila Martínez RJ, Mariscal de Alba A, Zuluaga Bedoya M, Marrón Fernández C, Trujillo MD, Rivas C, et al. Traqueotomias abiertas a pie de cama. <i>Rev patol respir</i> . 2016;19(2):44-7.	Excluded by title
32	Azaredo Bittencourt L, Luz G, Guimaraes T, Silva L, Badke L, Millani A, et al. Effect of treatment of mild obstructive sleep apnea on quality of life, mood and sustained attention: Randomized, parallel, single-blind and controlled study. <i>American Journal of Respiratory and Critical Care Medicine</i> . 2018;197(MeetingAbstracts).	Excluded by title
33	Azevedo KRS. Teste de broncodilatação: a incorporação de novos parâmetros na sua avaliação. <i>Pulmão RJ</i> . 2015;24(1):8-13.	Excluded by title
34	Azevedo MS, Machado AW, Barbosa Ida S, Esteves LS, Rocha VA, Bittencourt MA. Evaluation of upper airways after bimaxillary orthognathic surgery in patients with skeletal Class III pattern using cone-beam computed tomography. <i>Dental Press J Orthod</i> . 2016;21(1):34-41.	Excluded by title
35	Bacher M, Linz A, Buchenau W, Arand J, Krimmel M, Poets C, et al. [Treatment of infants with Pierre Robin sequence]. <i>Laryngorhinootologie</i> . 2010;89(10):621-9.	Excluded by title
36	Baha A, Ekici B, Ogan N, Akpınar EE. A case of sjögren's syndrome-related pulmonary arterial hypertension treated with Iloprost and Bosentan combination therapy. <i>Respiratory Case Reports</i> . 2018;7(2):59-62.	Excluded by title
37	Bartela TN. Treatment approaches to syndromes affecting craniofacial and dental structures. <i>Journal of the World Federation of Orthodontists</i> . 2019;8(4):131-7.	Excluded by title
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39	Baydur A. Recent developments in the physiological assessment of sarcoidosis: Clinical implications. <i>Current Opinion in Pulmonary Medicine</i> . 2012;18(5):499-505.	Excluded by title
40	Bedhet N, Mercier J, Gordeeff A, Mouzard A, Delaire J. [Labioglossopexy in Pierre Robin syndrome. Our experiences apropos of 70 cases]. <i>Rev Stomatol Chir Maxillofac</i> . 1990;91(5):326-34.	Excluded by title
41	Betancourt-Peña J, Tonguino-Rosero S. Impacto de la oxigenoterapia domiciliar en la capacidad funcional de pacientes con enfermedad pulmonar obstructiva crónica. <i>Rehabilitación (Madr, Ed impr)</i> . 2016;50(1):13-8.	Excluded by title
42	Bisinotto FMB, Seabra BC, Lóes FBP, Martins LB, Silveira LAMd. Postoperative angioedema induced by angiotensin-converting enzyme inhibitor: case report. <i>Rev bras anestesiologia</i> . 2019;69(5):521-6.	Excluded by title

43	Bitter N, Roeg D, Van Nieuwenhuizen C, Van Weeghel J. Training professionals in a recovery-oriented methodology: a mixed method evaluation. <i>Scandinavian journal of caring sciences</i> . 2019;33(2):457-66.	Excluded by title
44	Bjorklund KA, Billmire DA. Mandibular Body Resection and Setback for Severe Malocclusion in Lymphatic Malformations. <i>J Craniofac Surg</i> . 2016;27(3):724-6.	Excluded by title
45	Blanco Pérez JJ, Zamarrón Sanz C, Almazán Ortega R, García García M, López Castro J, Tumbeiro Novoa M. Síndrome de apnea del sueño en la insuficiencia cardíaca. Efecto de la presión positiva continua en la vía aérea. <i>An med interna (Madr)</i> . 1983; 2008;25(1):15-9.	Excluded by title
46	Borborema dos Santos VD, Assis GMD, Pereira da Silva JS, Rocha Germano A. Glossectomía parcial en paciente portador del síndrome de Beckwith-Wiedemann: relato del caso. <i>Rev esp cir oral maxilofac</i> . 2015;37(4):202-6.	Excluded by title
47	Borborema dos Santos VD, de Assis GM, da Silva JSP, Germano AR. Partial glossectomy in a patient carrier of Beckwith-Wiedemann syndrome: Presentation of a case. <i>Revista Espanola de Cirugia Oral y Maxilofacial</i> . 2015;37(4):202-6.	Excluded by title
48	Brogan WF. The stability of maxillary expansion. <i>Aust Dent J</i> . 1977;22(2):92-9.	Excluded by title
49	Bronfman CN. Avaliação das vias aéreas superiores por meio de tomografia computadorizada Cone-beam em pacientes Classe III submetidos à cirurgia bimaxilar. 2016:104-.	Excluded by title
50	Brunetto DP, Velasco L, Koerich L, Araujo MTD. Prediction of 3-dimensional pharyngeal airway changes after orthognathic surgery: A preliminary study. <i>American Journal of Orthodontics and Dentofacial Orthopedics</i> . 2014;146(3):299-309.	Excluded by title
51	Bruno LP, Motta JPS. Tratamento Endoscópico com Válvulas Endobrônquicas nos Pacientes com Enfisema Pulmonar. <i>Pulmão RJ</i> . 2017;26(1):39-44.	Excluded by title
52	Buchenau W, Wenzel S, Bacher M, Muller-Hagedorn S, Arand J, Poets CF. Functional treatment of airway obstruction and feeding problems in infants with Robin sequence. <i>Arch Dis Child Fetal Neonatal Ed</i> . 2017;102(2):F142-f6.	Excluded by title
53	Burgos MA, Sevilla García MA, Sanmiguel Rojas E, Pino Cd, Fernández Velez C, Piqueras F, et al. Cirugía virtual para pacientes con obstrucción nasal: empleo de un software basado en dinámica de fluidos (MeComLand(R), Digbody(R) & Noseland(R)) para documentar parámetros objetivos de flujo y optimizar resultados quirúrgicos. <i>Acta otorrinolaringol esp</i> . 2018;69(3):125-33.	Excluded by title
54	Bussoni MF, Guirado GN, Matsubara LS, Roscani MG, Polegato BF, Minamoto ST, et al. Diastolic function and functional capacity after a single session of continuous positive airway pressure in patients with compensated heart failure. <i>Clinics</i> . 2014;69(5):354-9.	Excluded by title
55	Butković D. Some pediatric syndromes with difficult airways in anesthesia induction. <i>Acta Medica Croatica</i> . 2018;72:47-56.	Excluded by title
56	C GPd, Saldías P F. Entrenamiento muscular inspiratorio en el paciente con enfermedad pulmonar obstructiva crónica. <i>Rev chil enferm respir</i> . 2011;27(2):116-23.	Excluded by title
57	Cabedo García VR, Rodrigo Garcés Asemany C, Cortes Berti A, Oteo Elso JT, Ballester Salvador JB. Eficacia de la utilización correcta de los dispositivos de inhalación en pacientes con enfermedad pulmonar obstructiva crónica: ensayo clínico aleatorizado. <i>Med clín (Ed impr)</i> . 2010;135(13):586-91.	Excluded by title
58	Cabral DMG, Abrahão Júnior LJ, Marques CHD, Pereira BdB, Pedrosa RC. Disfagia orofaríngea na doença de Chagas crônica: avaliação fonaudiológica, videofluoroscópica e esofagomanométrica. <i>Acta fisiátrica</i> . 2015;22(1).	Excluded by title
59	Cadenat H, Boutault F. Strategy of the Decision in Orthognathic Surgery Part 1. Importance of the Functional Factors for Choosing the Surgical Procedure Theoretical Study. <i>Revue de Stomatologie et de Chirurgie Maxillo-Faciale</i> . 1992;93(1):25-31.	Excluded by title
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61	Cakirer B, Kucukkeles N, Nevzatoglu S, Koldas T. Sagittal airway changes: rapid palatal expansion versus Le Fort I osteotomy during maxillary protraction. <i>Eur J Orthod</i> . 2012;34(3):381-9.	Excluded by title
62	Calabrese C, Corcione N, Rea G, Stefanelli F, Meoli I, Vatrella A. Impact of long-term treatment with inhaled corticosteroids and bronchodilators on lung function in a patient with post-infectious bronchiolitis obliterans. <i>J bras pneumol</i> . 2016;42(3):228-31.	Excluded by title
63	Call Mañosa S, Pujol Garcia A, Chacón Jordan E, Martí Hereu L, Pérez Tejero G, Gómez Simón V, et al. Plan de cuidados individualizado durante oxigenación con membrana extracorpórea. <i>Caso clinic. Enferm intensiva (Ed impr)</i> . 2016;27(2):75-80.	Excluded by title
64	Capan E, Ersu R, Kiyani E, Yener HM, Arman A, Kilicoglu H. Monoblock appliance for treatment of children with sleep disordered breathing. <i>American Journal of Respiratory and Critical Care Medicine</i> . 2015;191.	Excluded by title
65	Capan E, Kiyani E, Ersu R, Kilicoglu H. Monoblock appliance in children with obstructive sleep apnea is an effective treatment modality. <i>European Respiratory Journal</i> . 2014;44.	Excluded by title
66	Caprioglio A, Zucconi M, Calori G, Troiani V. Habitual snoring, OSA and craniofacial modification. Orthodontic clinical and diagnostic aspects in a case control study. <i>Minerva Stomatol</i> . 1999;48(4):125-37.	Excluded by title
67	Carlos-Villafranca Fd, Cobo-Plana J, Macías-Escalada E, Martínez J. Vía aérea difícil: interacciones entre ortodoncia y anestesiología. <i>RCOE, Rev Ilustre Cons Gen Col Odontól Estomatól Esp</i> . 2005;10(2):187-95.	Excluded by title
68	Carra MC, Lavigne G, Rompré P. Sleep bruxism and headache in adolescents. <i>Sleep Medicine</i> . 2011;12:S21.	Excluded by title
69	Casanueva FL, Alzérreca JA. Válvula nasal en rinoplastia. <i>Rev otorrinolaringol cir cabeza cuello</i> . 2017;77(4):441-8.	Excluded by title
70	Castrillo Tambay M, Zubillaga Rodríguez I, Sánchez Aniceto G, Gutiérrez Díaz R, Gutiérrez Díez M, Montalvo Moreno JJ. Distracción osteogénica mandibular en microrretrognatia severa del adulto. <i>Rev esp cir oral maxilofac</i> . 2005;27(4):231-7.	Excluded by title
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74	Chen F, Terada K, Hanada K, Saito I. Predicting the pharyngeal airway space after mandibular setback surgery. <i>J Oral Maxillofac Surg</i> . 2005;63(10):1509-14.	Excluded by title
75	Chen F, Terada K, Hua Y, Saito I. Effects of bimaxillary surgery and mandibular setback surgery on pharyngeal airway measurements in patients with Class III skeletal deformities. <i>Am J Orthod Dentofacial Orthop</i> . 2007;131(3):372-7.	Excluded by title
76	Chen H, Yagi K, Tsuda H, Almeida F, Lowe A. Klearwa yTM oral appliances for pediatric patients with retruded mandibles. <i>Canadian Respiratory Journal</i> . 2012;19(3):e39.	Excluded by title
77	Chen Q, Zhao Y, Qian Y, Lu C, Shen G, Dai J. A genetic-phenotypic classification for syndromic micrognathia. <i>J Hum Genet</i> . 2019;64(9):875-83.	Excluded by title
78	Choi JW, Park YJ, Lee CY. Posterior Pharyngeal Airway in Clockwise Rotation of Maxillomandibular Complex Using Surgery-first Orthognathic Approach. <i>Plast Reconstr Surg Glob Open</i> . 2015;3(8):e485.	Excluded by title
79	Choi SH, Kang DY, Kim YH, Hwang CJ. Severe skeletal Class III malocclusion treated with 2-stage orthognathic surgery with a mandibular step osteotomy. <i>Am J Orthod Dentofacial Orthop</i> . 2014;145(4 Suppl):S125-35.	Excluded by title
80	Chouard CH. Did Napoleon suffer from chronic rhonchopathy? <i>Acta Oto-Laryngologica</i> . 2017;137(4):361-4.	Excluded by title
81	Cifuentes J, Palisson F, Valladares S, Jerez D. Life-threatening complications following orthognathic surgery in a patient with undiagnosed hereditary angioedema. <i>J Oral Maxillofac Surg</i> . 2013;71(4):e185-8.	Excluded by title
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85	Cortes M, Gomez M, Park S, Singh D. A combined approach for upper airway remodeling for skeletal class iii malocclusion with complex OSA. <i>Sleep</i> . 2018;41:A206.	Excluded by title
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90	Dahy K, Takahashi K, Saito K, Kiso H, Rezk I, Oga T, et al. Gender differences in morphological and functional outcomes after mandibular setback surgery. J Craniomaxillofac Surg. 2018;46(6):887-92.	Excluded by title
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526	Oktay H, Ulukaya E. Maxillary protraction appliance effect on the size of the upper airway passage. <i>Angle Orthod</i> . 2008;78(2):209-14.	Excluded; no untreated Class III group
527	Onem Ozbilen E, Yilmaz HN, Kucukkeles N. Comparison of the effects of rapid maxillary expansion and alternate rapid maxillary expansion and constriction protocols followed by facemask therapy. <i>Korean J Orthod</i> . 2019;49(1):49-58.	Excluded; no untreated Class III group
528	Pamporakis P, Nevzatoglu S, Kucukkeles N. Three-dimensional alterations in pharyngeal airway and maxillary sinus volumes in Class III maxillary deficiency subjects undergoing orthopedic facemask treatment. <i>Angle Orthod</i> . 2014;84(4):701-7.	Excluded; no untreated Class III group
529	Sayinsu K, Isik F, Arun T. Sagittal airway dimensions following maxillary protraction: a pilot study. <i>Eur J Orthod</i> . 2006;28(2):184-9.	Excluded; no untreated Class III group
530	Akin M, Ucar FI, Chousein C, Sari Z. Effects of chincup or facemask therapies on the orofacial airway and hyoid position in Class III subjects. <i>J Orofac Orthop</i> . 2015;76(6):520-30.	Included
531	Baccetti T, Franchi L, Mucedero M, Cozza P. Treatment and post-treatment effects of facemask therapy on the sagittal pharyngeal dimensions in Class III subjects. <i>Eur J Orthod</i> . 2010;32(3):346-50.	Included
532	Balos Tuncer B, Ulusoy C, Tuncer C, Turkoz C, Kale Varlik S. Effects of reverse headgear on pharyngeal airway in patients with different vertical craniofacial features. <i>Braz Oral Res</i> . 2015;29.	Included
533	Cretella Lombardo E, Franchi L, Lione R, Chiavaroli A, Cozza P, Pavoni C. Evaluation of sagittal airway dimensions after face mask therapy with rapid maxillary expansion in Class III growing patients. <i>Int J Pediatr Otorhinolaryngol</i> . 2020;130:109794.	Included
534	Danaei SM, Ajami S, Etemadi H, Azadeh N. Assessment of the effect of maxillary protraction appliance on pharyngeal airway dimensions in relation to changes in tongue posture. <i>Dent Res J</i> 2018;15:208-14.	Included
535	Kilinc AS, Arslan SG, Kama JD, Ozer T, Dari O. Effects on the sagittal pharyngeal dimensions of protraction and rapid palatal expansion in Class III malocclusion subjects. <i>Eur J Orthod</i> . 2008;30(1):61-6.	Included
536	Menendez-Diaz I, Muriel J, Cobo JL, Alvarez C, Cobo T. Early treatment of Class III malocclusion with facemask therapy. <i>Clin Exp Dent Res</i> . 2018;4(6):279-83.	Included
537	Mucedero M, Baccetti T, Franchi L, Cozza P. Effects of maxillary protraction with or without expansion on the sagittal pharyngeal dimensions in Class III subjects. <i>Am J Orthod Dentofacial Orthop</i> . 2009;135(6):777-81.	Included
538	Tuncer BB, Kaygisiz E, Tuncer C, Yuksel S. Pharyngeal airway dimensions after chin cup treatment in Class III malocclusion subjects. <i>J Oral Rehabil</i> . 2009;36(2):110-7.	Included
539	Yagci A, Uysal T, Usumez S, Orhan M. Effects of modified and conventional facemask therapies with expansion on dynamic measurement of natural head position in Class III patients. <i>Am J Orthod Dentofacial Orthop</i> . 2011;140(5):e223-31.	Included

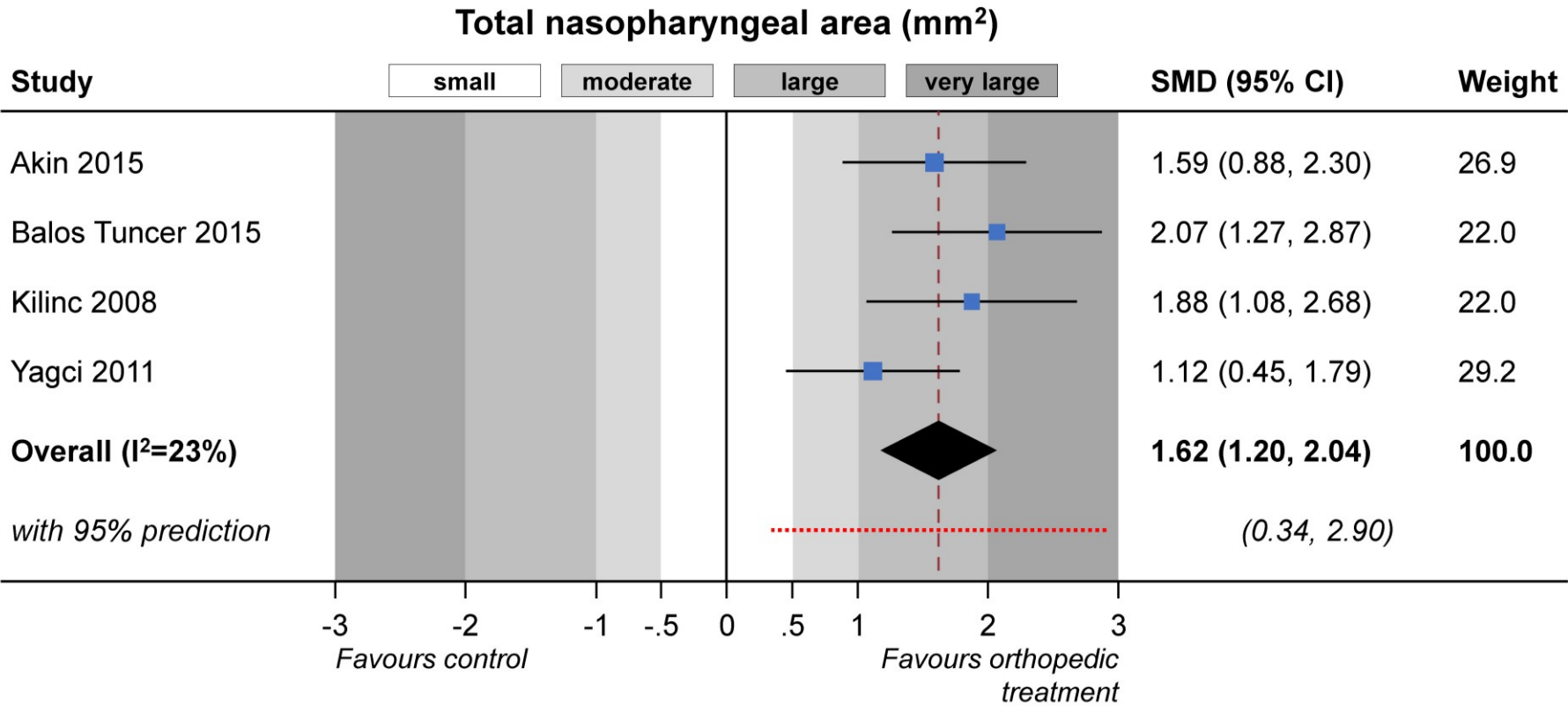
Supplementary Material S5. Results of individual studies comparing maxillary protraction to untreated controls that are not included in meta-analyses.

Nr	Study	Outcome*	MD (95% CI)	P	CR
1	Kilinc 2008	Total airway area (mm ²)	222.86 (14.04, 431.68)	0.04	Yes
2	Tuncer 2015	Nasopharynx: AA'-Pm' (mm)	1.55 (0.65, 2.46)	0.001	No
3	Tuncer 2015	Nasopharynx: Pm'-SPL (mm)	-1.25 (-2.37, -0.14)	0.03	No
4	Tuncer 2015	Nasopharynx: S-PNS (mm)	0.15 (-0.95, 1.25)	0.79	-
5	Mucedero 2009; Baccetti 2010	Nasopharynx: PNS-Ba (mm)	1.72 (0.24, 3.20)	0.02	No
6	Mucedero 2009; Baccetti 2010	Nasopharynx: PNS-H (mm)	1.41 (0.24, 2.59)	0.02	No
7	Mucedero 2009; Baccetti 2010	Nasopharynx: Ptm-Ba (mm)	1.34 (0.26, 2.42)	0.02	No
8	Tuncer 2015	Oropharynx: eb-Peb (mm)	1.25 (0.09, 2.41)	0.04	No
9	Tuncer 2015	Oropharynx: IPS (mm)	0.05 (-1.16, 1.26)	0.94	-
10	Tuncer 2015	Oropharynx: MPS (mm)	1.20 (0.39, 2.01)	0.004	No
11	Tuncer 2015	Oropharynx: AA-PNS (mm)	0.40 (-0.51, 1.31)	0.39	-
12	Tuncer 2015	Oropharynx: SPS (mm)	0.35 (-0.56, 1.26)	0.45	-
13	Tuncer 2015	Oropharynx: ve-Pve (mm)	1.05 (0.19, 1.91)	0.02	No
14	Kilinc 2008	Oropharynx: APW-PPW (mm)	1.27 (-0.83, 3.37)	0.24	-
15	Kilinc 2008	Oropharynx: APW'-PPW' (mm)	5.00 (0.75, 9.25)	0.02	Yes

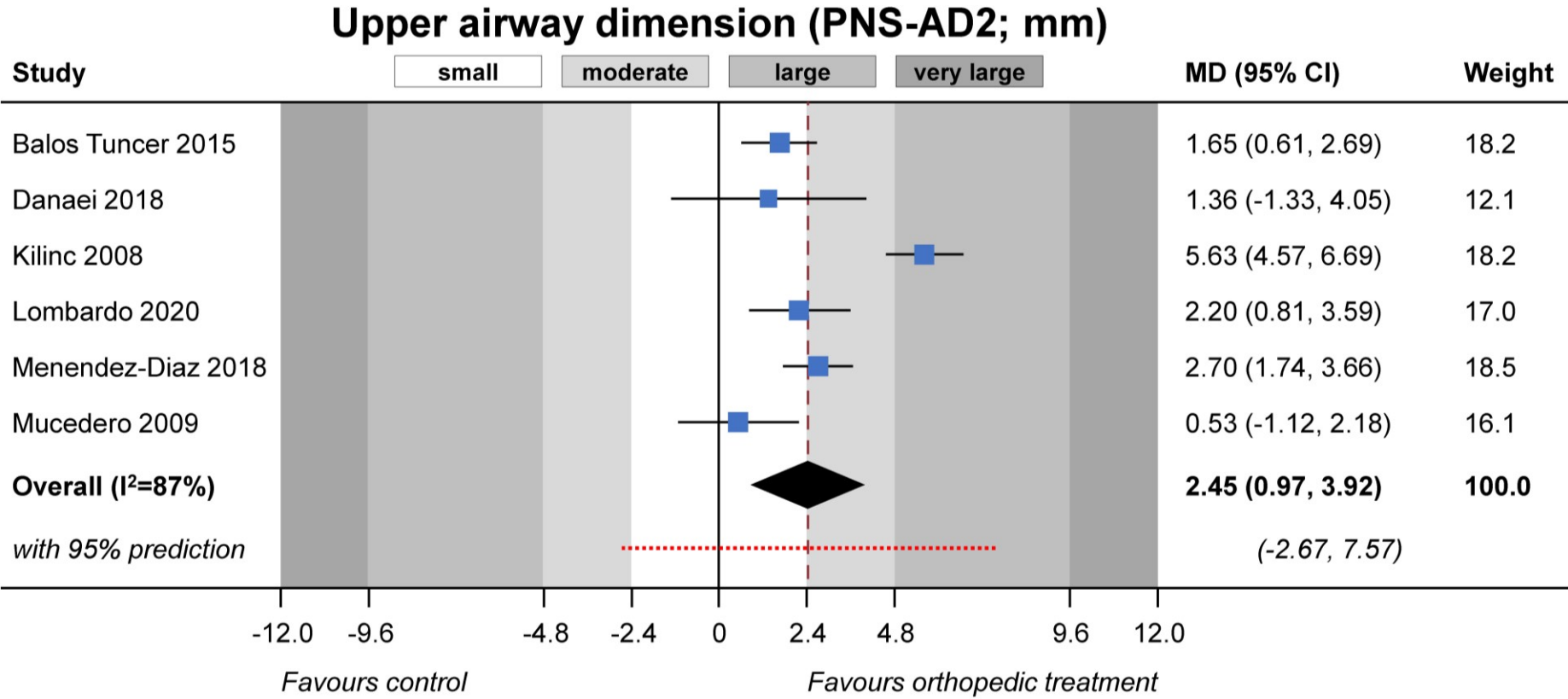
* from explanation of each landmark, consult the original studies.

CI, confidence interval; CR, clinically relevant (judged as effect being larger than one standard deviation of the control group pre-treatment); MD, mean difference.

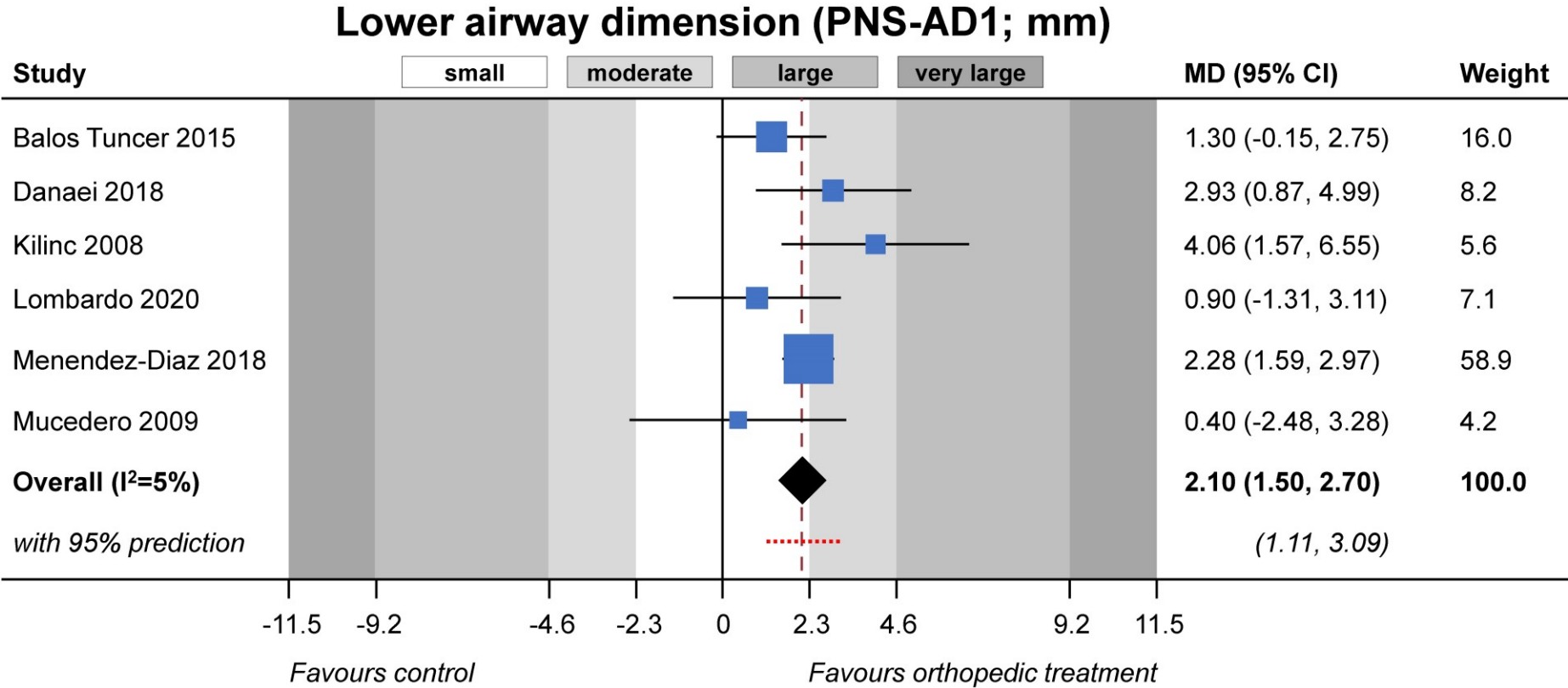
Supplementary Material S6. Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of total nasopharyngeal area.



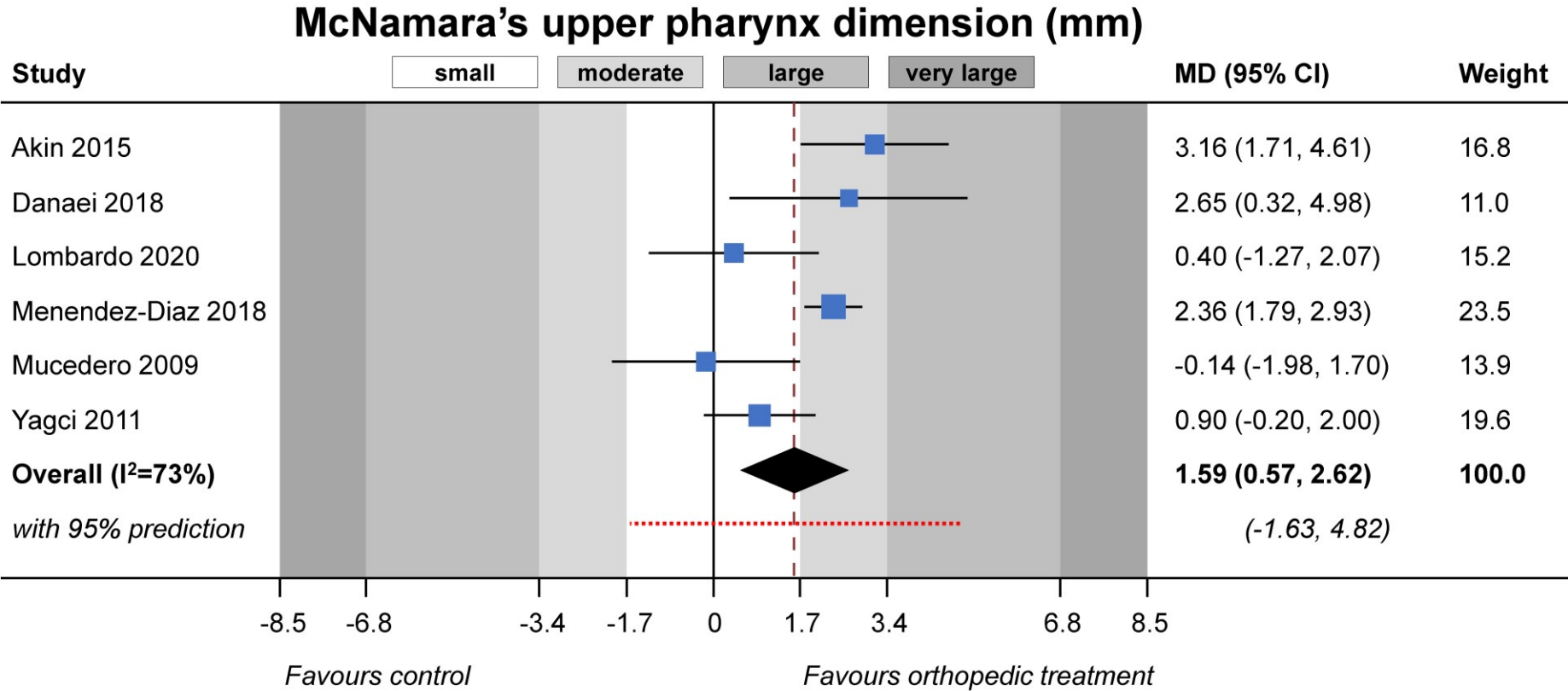
Supplementary Material S7. Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of upper airway dimension.



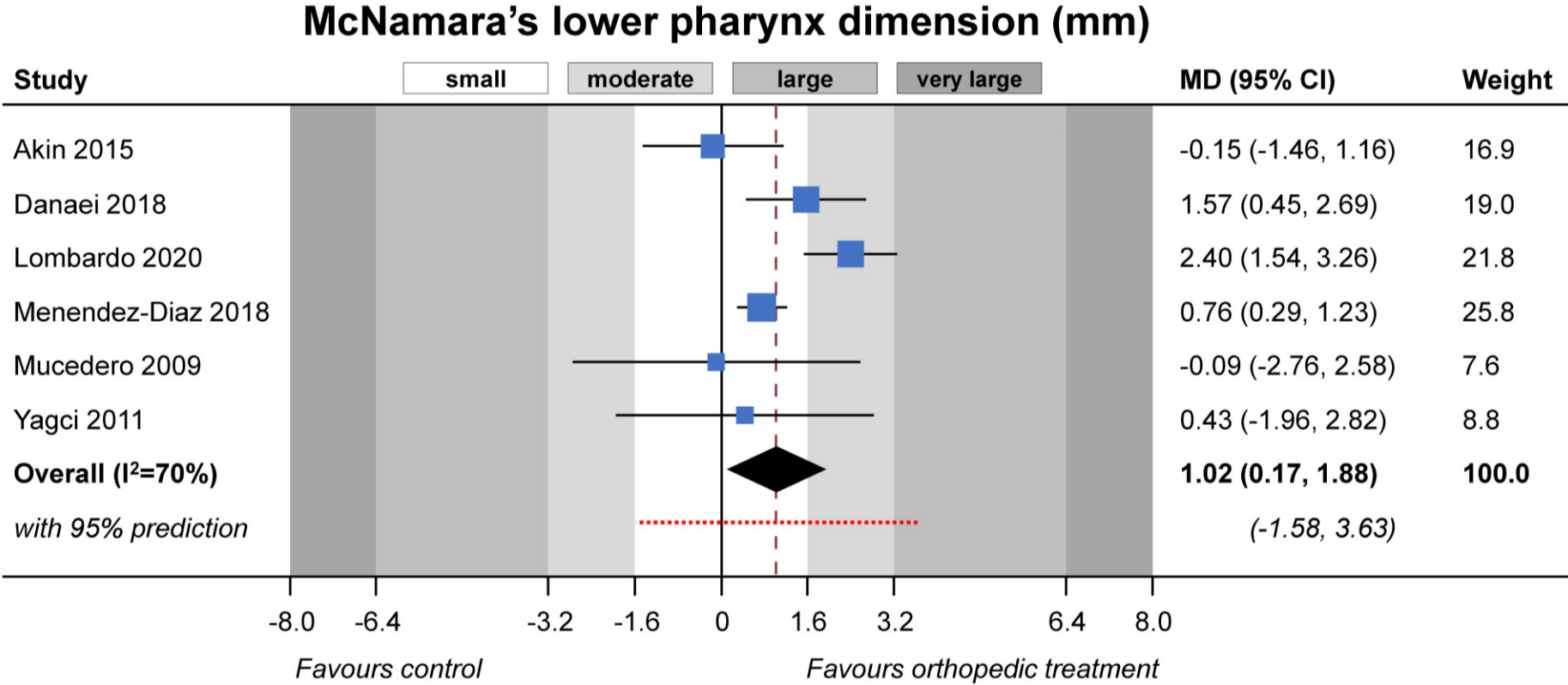
Supplementary Material S8. Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of lower airway dimension.



Supplementary Material S9. Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of McNamara’s upper pharynx dimension.



Supplementary Material S10. Contour-enhanced forest plot for the comparison of maxillary protraction with facemask versus changes in untreated controls in terms of McNamara's lower pharynx dimension.



Supplementary Material S11. Results of individual studies comparing chincup to untreated controls that are not included in meta-analyses.

Nr	Study	Outcome*	MD (95% CI)	P	CR
1	Akin 2015	Nasopharyngeal area (adenoidal) (mm ²)	12.29 (-16.22, 40.80)	0.40	-
2	Akin 2015	Nasopharyngeal area (aerial) (mm ²)	-3.22 (-44.23, 37.79)	0.88	-
3	Akin 2015	Nasopharyngeal area (total) (mm ²)	9.08 (-23.74, 41.90)	0.59	-
4	Tuncer 2009	Nasopharyngeal area (mm ²)	10183.00 (10074.25, 10291.75)	<0.001	Yes
5	Tuncer 2009	Nasopharynx: AA'-Pm' (mm)	0.75 (-0.38, 1.88)	0.19	-
6	Tuncer 2009	Nasopharynx: Pm'-SPL (mm)	-0.28 (-1.97, 1.41)	0.75	-
7	Tuncer 2009	Nasopharynx: PNS-AD1 (mm)	1.59 (-0.95, 4.13)	0.22	-
8	Tuncer 2009	Nasopharynx: PNS-AD2 (mm)	-0.20 (-2.42, 2.02)	0.86	-
9	Tuncer 2009	Nasopharynx: PNS-S (mm)	0.35 (-1.01, 1.71)	0.61	-
10	Tuncer 2009	Oropharyngeal area (mm ²)	-8231.00 (-10616.52, -5845.48)	<0.001	No
11	Tuncer 2009	Oropharynx: AA-PNS (mm)	-0.18 (-1.94, 1.58)	0.84	-
12	Tuncer 2009	Oropharynx: eb-Peb (mm)	1.62 (-1.23, 4.47)	0.27	-
13	Tuncer 2009	Oropharynx: IPS (mm)	1.66 (-0.67, 3.99)	0.16	-
14	Tuncer 2009	Oropharynx: MPS (mm)	0.79 (-0.76, 2.34)	0.32	-
15	Tuncer 2009	Oropharynx: SPS (mm)	1.13 (-0.48, 2.74)	0.17	-
16	Tuncer 2009	Oropharynx: ve-Pve (mm)	0.57 (-0.75, 1.89)	0.40	-
17	Akin 2015	Lower pharynx dimension (mm)	-0.40 (-1.68, 0.88)	0.54	-
18	Akin 2015	Upper pharynx dimension (mm)	-0.25 (-1.61, 1.11)	0.72	-

* from explanation of each landmark, consult the original studies.

CI, confidence interval; CR, clinically relevant (judged as effect being larger than one standard deviation of the control group pre-treatment); MD, mean difference.

Supplementary Material S12. Sensitivity analyses of meta-analyses post-treatment with at least 3 studies.

		Sample size			Baseline similarity (airways)		
	Original	Large	Small		Similar	Different	
Outcome	Effect (95% CI)	Effect (95% CI)	Effect (95% CI)	P	Effect (95% CI)	Effect (95% CI)	P
Total nasopharyngeal area – (mm ²)	n=4 SMD=1.62 (1.20, 2.04)	n=0	n=4	-	n=2 SMD=1.97 (1.41, 2.54)	n=2 MD=1.34 (0.86, 1.83)	0.1 4
Upper adenoid size (AD2-H; mm)	n=3 MD=0.59 (-0.52, 1.70)	n=3	n=0	-	n=3	n=0	-
Lower adenoid size (AD1-Ba; mm)	n=3 MD=0.12 (-2.20, 2.44)	n=3	n=0	-	n=3	n=0	-
Upper airway dimension (PNS- AD2; mm)	n=6 MD=2.45 (0.97, 3.92)	n=3 MD=1.95 (0.74, 3.16)	n=3 MD=3.00 (0.21, 5.79)	0.45	n=6	n=0	-
Lower airway dimension (PNS- AD1; mm)	n=6 MD=2.10 (1.50, 2.70)	n=3 MD=1.71 (0.50, 2.92)	n=3 MD=2.52 (0.90, 4.14)	0.84	n=6	n=0	-
McNamara's upper pharynx dimension (mm)	n=6 MD=1.59 (0.57, 2.62)	n=3 MD=1.07 (-0.55, 2.69)	n=3 MD=2.11 (0.58, 3.65)	0.90	n=4 MD=1.38 (0.04, 2.73)	n=2 MD=1.98 (-0.23, 4.19)	0.8 0
McNamara's lower pharynx dimension (mm)	n=6 MD=1.02 (0.17, 1.88)	n=3 MD=1.26 (-0.10, 1.88)	n=3 MD=0.70 (-0.52, 1.93)	0.75	n=4 MD=1.37 (0.43, 2.30)	n=2 MD=-0.02 (-1.17, 1.14)	0.3 4

CI, confidence interval; MD, mean difference; SMD, standardized mean difference.